Minako Aoki, MD
Takahide Teramoto, MD
Kentaro Omoya, MD
Department of Pediatrics
Graduate School of Medicine
Gifu University
Gifu, Japan
Naomichi Matsumoto, MD
Department of Human Genetics
Nagasaki University School of Medicine
Nagasaki, Japan
Department of Human Genetics
Yokohama City University Graduate School of Medicine
Yokohama, Japan
Naohiro Kurotaki, MD
Department of Human Genetics
Nagasaki University School of Medicine
Nagasaki, Japan
Department of Molecular and Human Genetics
Baylor College of Medicine
Houston, Texas
Osamu Shimokawa, MD
Department of Human Genetics
Nagasaki University School of Medicine
Nagasaki, Japan
Kyushu Medical Science Nagasaki Laboratory
Nagasaki, Japan
Kenji Kurosawa, MD
Division of Medical Genetics
Kanagawa Children's Medical Center
Yokohama, Japan
Naomi Kondo, MD
Department of Pediatrics
Graduate School of Medicine
Gifu University
Gifu, Japan

Received March 16, 2005. Received revised May 25, 2005. Accepted for publication July 26, 2005

Address correspondence to Dr Zenichiro Kato, Department of Pediatrics, Graduate School of Medicine, Gifu University, Yanagido 1-1, Gifu 501-1194, Japan. Tel: +81 (58) 230 6386; fax: +81 (58) 230 6387; e-mail: zen-k@cc.gifu-u.ac.jp.

References

1. Sotos JF, Dofge PR, Muirhead D, et al: Cerebral gigantism in childhood. *N Engl J Med* 1964;271:109–116.
2. Cole TRP, Hughes HE: Sotos syndrome: A study of the diagnostic criteria and natural history. *J Med Genet* 1994;31:20–32.
3. Kurotaki N, Imaizumi K, Harada N, et al: Haploinsufficiency of NSD1 causes Sotos syndrome. *Nat Genet* 2002;30:365–366.
4. Schaefer GB, Bodensteiner JB, Buehler BA, et al: The neuroimaging findings in Sotos syndrome. *Am J Med Genet* 1997;68:462–465.
5. Aoki N, Oikawa A, Sakai T: Serial neuroimaging studies in Sotos syndrome. *Neurol Res* 1998;20:149–152.
6. Inoue K, Kato S, Numaga J, et al: Optic disk pallor and retinal atrophy in Sotos syndrome. *Am J Ophthalmol* 2000;130:853–854.
7. Mizuno S, Nandate Y, Enya M, et al: Evalutaion of regional cerebral blood flow changes in normal aging using 99m-Tc-ECD SPECT and Patlak method. *Radioisotopes* 1998;47:392–398.
8. Danielsen ER, Ross B: *Magnetic Resonance Spectroscopy Diagnosis of Neurological Diseases*, 3rd ed. New York, Marcel Dekker, 1999.
9. Flippi CG, Ulug AM, Deck MD, et al: Developmental delay in children: Assessment with proton MR spectroscopy. *AJNR Am J Neuroradiol* 2002;23:882–888.
10. Rutter SC, Cole TR: Psychological characteristics of Sotos syndrome. *Dev Med Child Neurol* 1991;33:898–902.
11. Finegan JK, Cole TR, Kingwell E, et al: Language and behavior in children with Sotos syndrome. *J Am Acad Child Adolesc Psychiatry* 1994;33:1307–1315.
12. Mauceri L, Sorge G, Baieli S, et al: Aggressive behavior in patients with Sotos syndrome. *Pediatr Neurol* 2000;22:64–67.

Methadone Intoxication in a Child: Toxic Encephalopathy?

ABSTRACT

Methadone is used in the treatment of opioid addiction. Acute intoxication can lead to severe consequences and can even be lethal. In several case reports and small series, a presumably toxic leukoencephalopathy is described resulting from inhalation of heroin. We present the case of a 3-year-old boy who ingested methadone accidentally. In a coma with acute obstructive hydrocephalus owing to massive cerebellar edema and supratentorial lesions, he was successfully treated with methylprednisolone and cerebrospinal fluid external drainage. To our knowledge, this is the first report of an encephalopathy associated with synthetic opioid intoxication. (*J Child Neurol* 2006;21:618–620; DOI 10.2310/7010.2006.00146).

Many toxic effects of opioids have been reported; a toxic leukoencephalopathy resulting from heroin inhalation has been described, although the clinical and imaging findings are variable and the physiopathology remains unknown.[1]

Methadone is a synthetic opioid used for decades in the treatment of opioid addiction.[2] After ingestion, the effects appear within 30 minutes to 4 hours, and the average half-life is 23 to 25 hours, although central nervous system depressor effects can last longer (up to 48 hours).[2] Renal excretion is largely affected by the urinary pH (clearance is lower with alkaline urine).[2] Methadone has a great affinity with the mu class of opioid receptors and binds weakly to the kappa and delta receptors (a binding profile similar to that of morphine).[1,2] We present one case of methadone intoxication and acute leukoencephalopathy with a predominant cerebellar lesion with total recovery.

Case Report

A 3-year-old male child was referred to our hospital in a coma. Both parents were opioid addicted and under a treatment program with methadone. This child had no relevant history other than methadone exposure in utero and neonatal withdrawal syndrome. The child was found unconscious in bed. On arrival at the emergency department, the child was in a coma with irregular breathing and low blood pressure (48/28 mm Hg). The axillary temperature was 34.7°C. He had no signs of trauma. Blood glucose was 490 mg/dL and blood pH was 6.87 with 11 mEq/L bicarbonate (capillary blood). He was ventilated and volume expanded; bicarbonate, dopamine, and ceftriaxone were administered. After stabilization of vital signs, he was referred to our hospital's intensive care unit. By this time, the patient reacted only to pain, bilaterally, with a slow and generalized symmetric extensor posture. His pupils were myotic. Oculocephalic reflexes were absent. Capillary blood pH was 7.56 with 23.5 mEq/L bicarbonate. The urine test for methadone was negative, but naloxone was administered owing to a high clinical suspicion. The patient responded with eye opening and a few spontaneous movements of the limbs but returned quickly to his previous neurologic state.

A computed tomographic (CT) scan (5 hours after arrival at hospital) revealed an extensive bilateral and symmetric hypodensity of

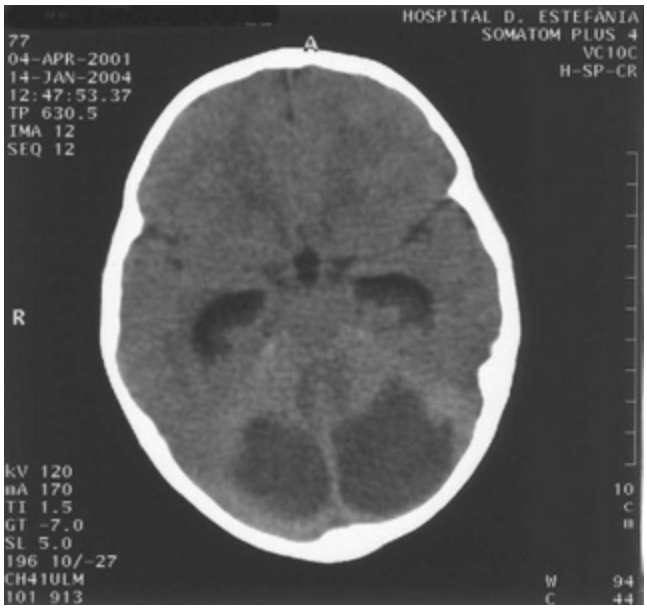

Figure 1. A computed tomographic (CT) scan 5 hours after admission shows severe cerebellar edema, effacement of perimesencephalic cisterns, and a slightly enlarged third ventricle and temporal horns of lateral ventricles, indicating acute hydrocephalus.

the cerebellar hemispheres and pons with some inferior displacement of the cerebellar amygdala and slightly enlarged temporal horns, indicating acute hydrocephalus.

The patient's head was raised, and mannitol and dexamethasone were administered. Thirty-six hours after admission, methadone testing in the urine was positive, when the urinary pH was 5. The clinical picture remained unchanged. The repeated CT scan revealed the same findings (paramesencephalic and prepontine cisterns and cisterna magna totally occupied by the enlarged cerebellum and brain stem) (Figure 1).

Surgical treatment of the patient's acute hydrocephalus was undertaken with ventricular cerebrospinal fluid external drainage in the Santa Maria Hospital. The patient recovered consciousness promptly, remaining in a state of mutism and right-sided hemiplegia. In the next few days, the hemiplegia disappeared and limb and truncal ataxia became apparent, with mutism replaced by slow, low-pitched, dysarthric speech.

On the sixth day in hospital, cerebral magnetic resonance imaging (MRI) confirmed the cerebellar lesions and revealed additional bilateral lesions in the hippocampus (Figure 2). The patient was then treated with a high dosage of methylprednisolone (30 mg/kg/day) for 3 days. The ventricular catheter was removed on the eleventh day. The patient left hospital on the sixteenth day still exhibiting a residual ataxia, which resolved in the subsequent 4 weeks.

Discussion

Methadone intoxication was confirmed only after repeated testing. Overcorrection of the acidosis led to alkaline urine and negative testing for methadone. Therefore, naloxone can be used as a diagnostic and therapeutic trial. The response to naloxone was equivocal, and the patient's CT scan revealed a prominent cerebellar lesion and acute hydrocephalus, raising additional diagnostic questions.

Severe opioid intoxication causes coma with myosis and suppression of brainstem reflexes (oculocephalic responses are usually absent).[1,3] A cerebellar and brainstem structural lesion can have a very

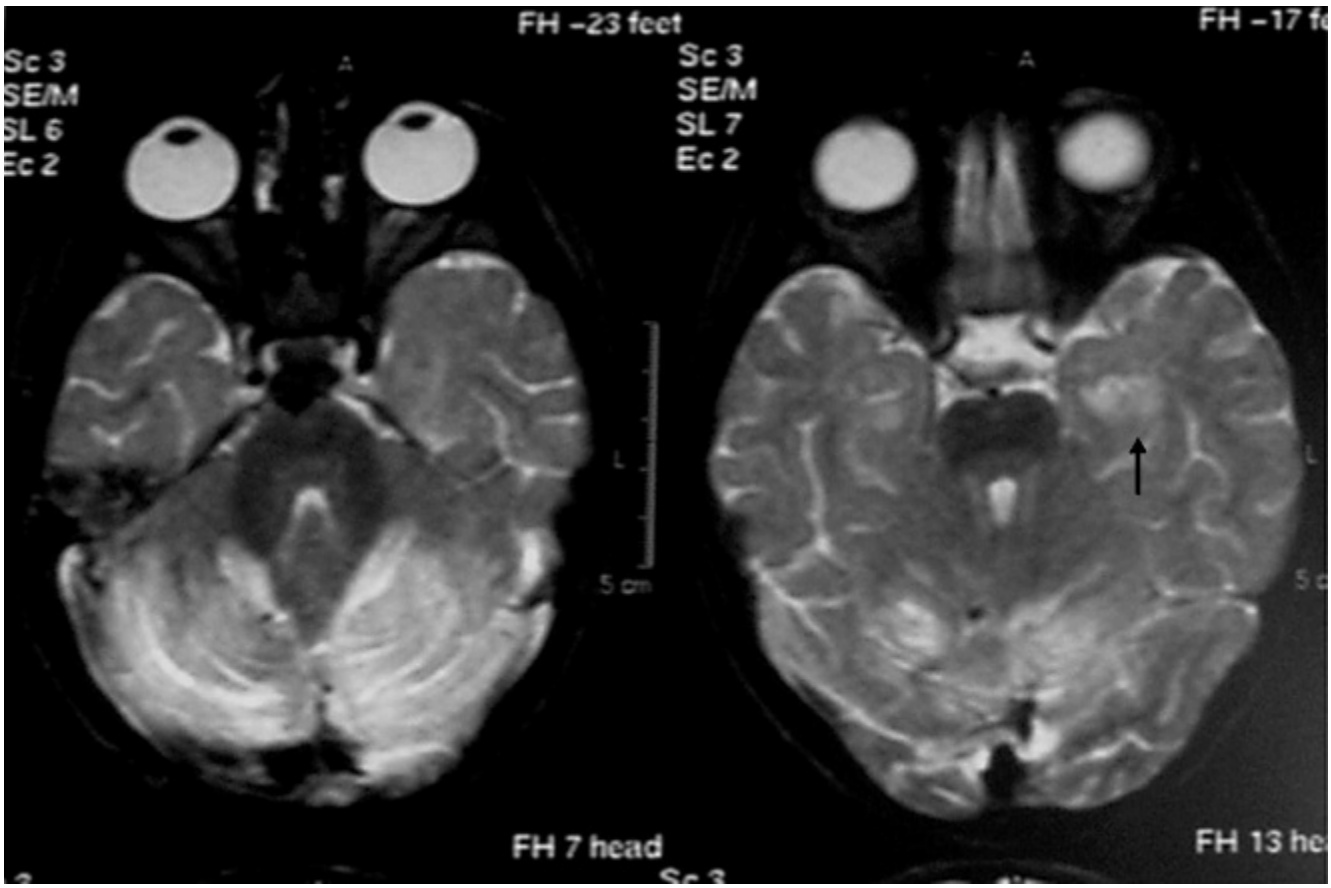

Figure 2. A T_2-weighted magnetic resonance image (MRI) performed on the sixth day in hospital still reveals an abnormal hyperintense signal in the cerebellar hemispheres and hippocampus, bilaterally, but more evident on the left side (*arrow*).

similar clinical presentation: coma with small pontine pupils and early and pronounced suppression of brainstem reflexes.

Hypoxia or ischemia would lead to very different radiologic and clinical findings, but we cannot exclude the fact that it might have had an enhancing effect on this probably toxic encephalopathy. A presumably infectious or immunologic cerebellitis has been reported with cerebellar edema—hypodense lesions on CT or hyperintense lesions on T_2-weighted MRI—but our patient had no clinical or laboratory evidence of a previous or concomitant infection.

Some reports and case series describe a toxic leukoencephalopathy in heroin inhalers.[1,3] This disorder of unknown etiology affects the cerebellar white matter; lesions in the supratentorial white matter are also prominent. Reported symptoms are progressive dementia and ataxia with pyramidal signs. Nevertheless, acute encephalopathy with depressed consciousness and ataxia can also occur.[3] Almost all patients were heroin inhalers, except one child who ingested heroin accidentally and had a reversible leukoencephalopathy with an extensive cerebellar lesion.[4] Contamination of heroin by other toxic products was never found and seems unlikely at present. Some patients were studied with magnetic resonance spectroscopy. The magnetic resonance spectroscopic pattern suggested axonal injury without demyelination. A lactate peak raised the question of mitochondrial dysfunction.[3] In some cases, the disease had a fatal evolution and neuropathologic examination revealed spongiform leukoencephalopathy with intramyelinic edema, an unchanged blood–brain barrier, and relative axonal and myelin sheath preservation.[3]

Our patient ingested methadone (not a "street" drug) accidentally, and the question of contamination with other toxics was not relevant. He had an encephalopathy that was in many aspects similar to some previously reported cases of heroin leukoencephalopathy. Methadone has a pharmacologic profile similar to that of morphine, including a great affinity to mu receptors and weak binding to delta and kappa receptors.[2] Studies on opioid receptors have led to the conclusion that the cerebellum and limbic system have the greatest density of opioid receptors, although with a variable expression of different subtypes of receptors.[5] The cerebellum is thought to have mostly mu and, in a lesser amount, delta receptors and probably does not express kappa receptors. The role of these receptors in physiologic, therapeutic, or toxic situations is not known.[5] Stimulation of opioid receptors can lead to a state of cellular energy deprivation, and hypoxia and/or acidosis might enhance this effect.[3]

This case allows us to speculate that several drugs of this class (not only heroin) and several routes of intoxication (not only inhalation) can lead to opioid leukoencephalopathy. To our knowledge, this is the first reported case of encephalopathy related to exposure to a synthetic opioid. Overdose with this class of drugs is a quite common event, so some unrecognized individual susceptibility factors could account for the relative rarity of this disorder.

Marisol Anselmo, MD*
Intensive Care Unit
Hospital de Dona Estefânia
Lisbon, Portugal
António Campos Rainho, MD*
Neurosurgery Department
Hospital de Santa Maria
Lisbon, Portugal
Maria do Carmo Vale, MD
João Estrada, MD
Rosalina Valente, MD
Intensive Care Unit
Hospital de Dona Estefânia
Lisbon, Portugal
Manuela Correia, MD
Intensive Care Unit
Pediatric Department
Hospital de Santa Maria
Lisbon, Portugal
José Pedro Vieira, MD
Neurology Department
Hospital de Dona Estefânia
Lisbon, Portugal
Deolinda Barata, MD
Intensive Care Unit
Hospital de Dona Estefânia
Lisbon, Portugal

Received May 26, 2005. Received revised July 27, 2005. Accepted for publication July 31, 2005

*First authors who contributed equally to this study.

Address correspondence to Dr. José Pedro Vieira, Departamento de Neurologia, Hospital de Dona Estefânia, Rua Jacinta Marto, 1159-045 Lisbon, Portugal. Tel: + 21 301 69 74; fax: + 21 312 69 63; e-mail: hde.neuro@mail.telepac.pt.

References

1. Wolters EC, Wijngaarden GK, Stam FC, et al: Leucoencephalopathy after inhaling "heroin" pyrolysate. *Lancet* 1982;2:1233–1237.
2. Dart RC: Methadone, in Dart RC (ed): *Medical Toxicology*, 3rd ed. Philadelphia, Lippincott William & Wilkins, 2004, 767–768.
3. Vella S, Kreis R, Lovblad KO, Steinlin M: Acute leukoencephalopathy after inhalation of a single dose of heroin. *Neuropediatrics* 2003;34:100–104.
4. Roulet Perez E, Maeder P, Rivier L, Deonna T: Toxic leucoencephalopathy after heroin ingestion in a 2½ -year-old child. *Lancet* 1992;340: 729.
5. Shadrack J, Willoch F, Platzer S, et al: Opioid receptors in the human cerebellum: Evidence from (^{11}C) diprenorphine PET, mRNA expression and autoradiography. *Neuroreport* 1999;10:619–624.

Electroencephalographic (EEG) Findings in Posterior Reversible Encephalopathy Associated With Immunosuppressants

ABSTRACT

Posterior reversible encephalopathy has been reported in patients who receive immunosuppressants. Compared with radiologic studies, electroencephalographic (EEG) findings are not well described. We performed EEG serially in three children who suffered from posterior reversible encephalopathy associated with tacrolimus or cyclosporine. EEG showed continuous focal rhythmic activities in the acute period. EEG findings normalized after the clinical manifestations had disappeared. We conclude that EEG is useful for the diagnosis and follow-up of posterior reversible encephalopathy. (*J Child Neurol* 2006;21: 620–623; DOI 10.2310/7010.2006.00147).

It has been reported that treatment with immunosuppressive agents induces encephalopathy in transplant patients.[1–7] Magnetic resonance imaging (MRI) often shows multiple bilateral lesions in the posterior part of the cerebrum. This condition has been called "posterior reversible encephalopathy syndrome." Although clinical and radiologic findings have been well recognized,[1,2,5–8] electroencephalographic (EEG) findings have not been extensively reported. We performed EEG serially in three children who suffered from posterior reversible encephalopathy associated with immunosuppressants between 1999 and 2002, and compared the findings with their clinical manifestations.